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PROPOSED TEST PLAN FOR ZINC NAPHTHENATE

CASRN 12001-85-3

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on Behalf of:

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Summary

Zn naphthenate is one of 19 metal carboxylate chemicals organized under the Metal Carboxylates Coalition (The Coalition), an HPV testing consortium managed by the Synthetic Organic Chemical Manufacturers Association's (SOCMA) VISIONS Department. The company sponsoring this chemical is OM Group, Inc. HPV endpoints for Zn naphthenate are filled using a comprehensive existing data set for the metal salt, which is a registered pesticide under the Federal Insecticide Fungicide and Rodenticide Act (FIFRA). In addition, the metal salt data are supported by data for its dissociations products because metal carboxylates such as Zn naphthenate readily dissociate into the corresponding metal and carboxylic acid,. Therefore, robust summaries are provided for the parent compounds (Zn naphthenate), as well as the metal (Zn) and the acid (naphthenic acid). Selected testing of the parent compound has been proposed to fill HPV endpoints not filled by the existing FIFRA data. The summary of existing data and proposed testing is presented below and summarized in the Test Plan Matrix (Table 1)

Use Patterns for Metal Carboxylates

The metal carboxylates function to deliver a metal ion into chemical reactions. The carboxylic acids (acids) are designed for use in different products or chemical reactions. Zinc carboxylate compounds are used as catalysts in paints and coatings; and in polyurethanes. They are used as heat stabilizers for PVC and as a heat and/or friction modifiers for lubricants and greases. Zinc carboxylate compounds can also be used as wetting agent for pigments in organic systems. Zinc naphthenate is registered as a fungicide/wood preservative.

Characteristics of Zn Naphthenate

The metal carboxylate salts are designed to deliver metals to chemical reactions; therefore, they are designed to readily dissociate into the free metal and free acid. The dissociation constant is important because it determines the proportion of acid or metal that is dissociated at a given pH. The properties of the free acid and corresponding free metal are often much different than those of the salt (ion pair) moiety for characteristics such as solubility, adsorption, and toxicity. The proportion of dissociation is determined by pH. The amount of dissociation influences the behavior of the substance in the environment and bioavailablity of the acid and metal constituents of metal carboxylate salts. The lower dissociation constant (pKa) for Zn naphthenate is 7.31, which means that, at this pH, 50% of the Zn naphthenate molecules are dissociated into the metal and organic moieties, while 50% remain as associated complexes (parent). The proportion of dissociation increases with decreasing pH, with approximately 90% dissociation occurring at a pH of one unit below the pKa..

There are two forms of Zinc naphthenate available, a viscous liquid containing 8-10% zinc or a solid containing 16% zinc (EPA 1992). The commercial products are complex mixtures of naphthenates with variable size and structural composition as they recovered as petroleum distillate fractions, then reacted with zinc. The molecular weight of individual Zn naphthenates range from approximately 381 to 813. Their general molecular formula is described as:

$$Zn(MRCO_2)(NRCO_2)$$

Where, R = alkyl group with a chain length of 0 to 10 carbon atoms. M & N are typically one or two fused rings (usually cyclopentane, but occasionally cyclohexane and heptane rings) that may contain one or more alkyl substitutions. The total number of carbon atoms in M or N ranges from about 9 to 25. In some cases, no fused ring is present and M or N may be straight-chain or multiple branched carbon/hydrogen/oxygen molecules.

Dissociation Products

This submission relies primarily on the existing FIFRA data set for Zn naphthenate. However, because the dissociation products (metal and acid) are important to understanding the environmental fate and effects of the parent metal carboxylate, robust summaries for the dissociation products are provided as part of this submission. The zinc dossier (i.e., robust summaries) contains I data primarily for Zn chloride (CAS No. 7646-85-7). This salt is a readily dissociable source of Zn with an anion that is not toxic. It is highly soluble in water and therefore probably represents the most bioavailable (and toxic) form of zinc. A complete as possible naphthenic acids robust summary is also provided as part of this submission.

Summary of Existing Data

The existing data is summarized in Table 2. The data is derived primarily from the FIFRA dataset, which supports a current registration of Zn naphthenate as a fungicide. This data has been reviewed by the U.S. EPA Office of Pesticide Programs and accepted as part of the registration process.

Physicochemical Properties

A distinct melting point would not be expected for Zn naphthenate due its complex chemical composition. Existing data are available for boiling point, vapor pressure and partition coefficient. Water solubility is currently being tested. The low vapor pressure (< 1.0 mm Hg) indicates a low tendency to vaporize. The log partition coefficient of 1.10 is very low indicating little or no potential for significant bioaccumulation. There are inherent difficulties in measuring the partition coefficient due to the complex composition and aquatic chemistry of this substance. Although this study is rated as reliable with restrictions, the study did not measure the partition coefficient at different pHs, which would make the data easier to interpret.

Environmental Fate Parameters

Dissociation constants have recently been determined for this and other metal carboxylates supported by the Metal Carboxylates Coalition. The pKa values for Zn napthenate were 7.31 (SD = 0.0131) and 9.18 (SD = 0.0466). This indicates that Zn naphthenate will be 50% dissociated into an ionized metal moiety and ionized organic acid at a pH of 7.31. Because Zn is divalent and Zn naphthenate has two moles of naphthenic acid per mole of Zn, there is a second dissociation point (i.e., pH 9.18) where the metal moiety will dissociate from the second mole of naphthenate. In addition to the heterogeneity of the metal, metal organic and organic acid in solution, naphthenic acid is not a single pure chemical, but a complex distillate fraction. The naphthenic acid portion of the molecule is a mixture of related compounds with variation in the ring structures and the length of side chains. For a chemical with this combination of characteristics (e.g., partially dissociated at environmental pH with dissociation products that are ionizable and not single, pure compounds) makes the use of environmental (fugacity) modeling impossible. Therefore, no transport (fugacity) modeling is reported and no testing is recommended. Similarly, photodegradation cannot be determined or modeled due to the characteristics of this substance(i.e., dissociable and an acid that is not a single compound). Zn naphthenate has not been assessed for biodegradability and the metal portion of the compound will not biodegrade. However, the acid (naphthenic acids) portion of Zn naphthenate was been reported to biodegrade. Fifty percent of naphthenate (sodium salt) was reported to be mineralized to CO_2 in 24-days by microbial populations indigenous to oil sands tailings (Herman et al. 1994)

Ecotoxicity

As shown in Table 2, ecotoxicity data are available for two fish species and one aquatic invertebrate species. Acute toxicity values for bluegill, trout, and *Daphnia* range from 1.1 to 4.6 mg/L and are considered moderately toxic (EPA 1985). Data for the aquatic plants are not available for the Zn naphthenate, and although there is data for the dissociation products individually, these data do not adequately fill this data element. The toxicity of naphthenic acids to *Navicula seminulum* was reported to be low ranging from 30.5-80.5 mg/L (EC50) based on growth (EPA 2002). In contrast, the 96-h EC50 of Zn (as ZnCl) to *Selenastrum capricornutum* was 0.0447 mg Zn/L. A similar value of 0.142 mg/Zn/L was reported for *Skeletonema costatum* (72-h EC50). Because theses species appear to be very sensitive to Zn, an algal toxicity study on Zn naphthenate is recommended.

Human Health Effects

The human health studies include a complete set of acute toxicity studies: acute oral, inhalation, and dermal toxicity, as well as skin and eye irritation (See Table 2). These studies are required under FIFRA and were tested on the formulated product, Fungitrol Zinc 8% fungicide. The three studies (oral, inhalation, and dermal) are all limit tests indicating a low order of toxicity when these routes exposure are used. In addition to the oral LD50 study with Fungitrol Zinc 8% fungicide, there are two additional rat oral LD50 studies with Zn naphthenate, which also show minimal toxicity in limit tests (LD50 values >5,000 mg/kg and >6,000 mg/kg) corroborating the low order of toxicity in the FIFRA studies. Finally data is available for skin and eye irritation.

The genetic toxicity studies, including a mutagenicity study (mouse lymphoma assay) and a chromosomal aberration study with Chinese hamster ovary cells, produced positive results both with and without metabolic activation (see Table 2). However, an unscheduled DNA synthesis study with primary hepatocytes gave negative results. All the available genetic toxicity studies were rated as reliable without restriction. As summarized in the Zn (chloride) robust summaries, this metal alone has been shown to be clastogenic and possibly weakly mutagenic.

The toxicity of Zn naphthenate after repeated doses has been assessed in a 90-d dermal exposure study with rabbits (see Table 2). The reported NOAEL and LOAEL values were 300 and 1,000 mg/kg/day, respectively. No effects on mortality were observed. Effects reported consisted of skin irritation including moderate to severe grades of erythema and edema as well as fissuring. No severe signs of skin irritation such as eschar and blanching were observed. Histopathological changes were observed in skin at the site of application. Mean body weights in the high treatment animals (1,000 mg/kg/day) were statistically lower than controls for males and females, but kidney and adrenal weights were higher than controls. Finally clinical chemistry revealed no statistically significant changes with the exception of a slight increase in neutrophils at the high dose level. This study was rated as reliable without restriction.

Zn naphthenate was determined not to be teratogenic or cause developmental toxicity at doses that were not maternally toxic following oral exposure during days 6 through 15 of gestation (see Table 2). The NOAEL was 188 mg/kg/day. In a second study in rats, oral exposure to Zn naphthenate resulted in no effects on intrauterine growth or survival. Clinical signs of toxicity consisted of anogenital and/or urogenital staining in the high and medium dose level. No effects were observed on body weight, but a slight effect on food consumption was observed.

The NOAELs for maternal toxicity and teratogenicity were 250 and 500 mg/kg/day, respectively. Both of these studies were reliable without restriction. Finally, in a two-generation study using oral administration in rats Zn naphthenate was found not to produce adverse effects on reproduction at exposure levels that were not maternally or paternally toxic. The NOAEL was reported as 1,000 mg/kg/day in the diet.

Test Plan Summary and Conclusions:

The test plan and summary conclusions made by the Coalition are summarized in the Test Plan Matrix (Table 1). The Coalition has proposed the following:

Physicochemical Properties

Adequate data available for the physicochemical properties (Test Plan Matrix, Table 1) with the exception of water solubility, which is currently being determined. No additional testing is recommended.

Environmental Fate Parameters:

Biodegradation: An evaluation of the biodegradation of Zn naphthenate is unnecessary. The parent, metal salt, dissociates into Zn, which does not biodegrade, and naphthenic acid, which is known to biodegrade (Hemen et al. 1994). Therefore, the Coalition will depend on the existing data for naphthenic acid to fill this data element and no testing is planned.

Photodegradation: In solution at environmental pHs, Zn naphthenate will dissociate to a significant degree. Zn will not photodegrade. Naphthenic acid is a complex distillate fraction for which photodegradation cannot be reliably estimated or accurately measured, therefore, this data element will not be filled. No testing is recommended.

Transport: Fugacity models rely upon a compound being pure and non-ionized and are inappropriate for a metal carboxylate such as Zn naphthenate, which dissociates into ionized moieties. In addition, because naphthenate is not a pure chemical, but rather a complex petroleum distillate fraction, modeling cannot be used to accurately and reliably predict transport. Fugacity modeling is designed for unionized, pure compounds and thus is considered inappropriate for Zn naphthenate and its dissociation products.

Ecotoxicity:

Adequate ecotoxicity data are available for fish and invertebrate species for Zn naphthenate; however, data for aquatic plant (green algae) toxicity are needed. No data for the acid (naphthenic acid) is available and data for Zn indicates algae may be more sensitive to this metal than the aquatic animal species (i.e., fish and invertebrates; therefore, testing is recommended for the algal toxicity endpoint (Test Plan Matrix Table 1).

Human Health Effects:

Because Zn naphthenate is a FIFRA registered product, results of a complete set of GLP studies that have been reviewed and accepted by the EPA are available, including studies for acute mammalian (oral, inhalation, dermal, skin irritation, eye irritation) toxicity studies and genotoxicity (gene mutation and chromosomal aberration). Higher tiered mammalian studies (i.e., repeated dose, reproduction, and developmental toxicity) are also available for Zn naphthenate; therefore, no additional human health effects studies are proposed for this chemical (Test Plan Matrix, Table 1l).

Conclusions:

In summary, the only data elements that need to be filled for Zn naphthenate are water solubility (currently underway) and algal toxicity for which testing is recommended .

References

EPA 1985. Hazard Evaluation Division, Standard Evaluation Procedure, Acute Toxicity Test for Aquatic Invertebrates, Washington, DC EPA-540/9-85-005.

EPA. 2002. ECOTOX Database System. Version 2.0. Available: http:/www.epa.gov/ecotox

Herman et al. 1994. Biodegradation of naphthenic acids by microbial populations indigenous to oil sands tailings. Can. J. Microbiol. 40:467-477)

Rockhold, W.T. 1955. Toxicity of naphthenic acids and their metal salts. A.M.A. Arch. Indust. Health. 12: 477-482.

Table 1 Test Plan Matrix: Zn Naphthenate

	Information available	GLP Study	Information for Dissociation Products	Acceptable	Testing recommended
PHYSICOCHEMICAL PROPERTIES					
Melting Point	Y	Y	N	Y	N
Boiling Point	Y	Y	N	Y	N
Vapor pressure	Y	U[a]	N	Y	N
Partition Coefficient	Y	Y	N	Y	N
Water Solubility	Y	Y	Y	Y	N
ENVIRONMENTAL FATE PARAMETERS					
Photodegradation	N	--[b]	--	--	N
Dissociation in water	Y	Y	--	Y	N
Transport	--	--	--	--	N
Biodegradation	N	--	Y	Y	N
ECOTOXICITY					
Fish toxicity (96-h)	Y	Y	Y	Y	N
Invertebrate toxicity (48-h	Y	Y	Y	Y	N
Algae toxicity (72-h)	N	--	Y	N	Y
TOXICITY					
Acute	Y	N	Y	Y	N
Repeated dose	Y	Y	N	Y	N
Genetic Toxicology – mutation assay	Y	Y	Y	Y	N
Genetic Toxicology – chromosomal aberration	Y	Y	Y	Y	N
Reproductive	Y	Y	Y	Y	N
Developmental	Y	Y	Y	Y	N

[a] U = undetermined
[b] -- means not applicable

Table 2 Summary of Existing Data

		REPORTED VALUES
SIDS ENDPOINT	**TEST/SPECIES**	**ZN NAPHTHENATE**
Physicochemical Properties		
Melting Point	NA	--
Boiling Point		116 °C
Vapor pressure		< 1.0 mm Hg
Log Partition Coefficient		1.10 @ 20 °C
Water Solubility		80 mg/L @ 20 °C
Environmental Fate Parameters		
Photodegradation	NA	--
Dissociation in water		7.13 and 9.18 @ 20 °C
Transport	NA	--
Biodegradation		50% degradation to CO_2 in 24 d (based naphthenic acid)
Ecotoxicity		
Fish toxicity (96-h)	Bluegill Trout	1.5 mg a.i./L 1.1 mg a.i./L
Invertebrate toxicity (48-h)	*Daphnia*	4.6 a.i./L
Algae toxicity (96-h)		No data
Human Health Effects		
Acute	Oral LD50, rat	>5,000 mg/kg
	Inhalation LC50, rat	>11.6 mg/L
	Dermal LD50, rabbit	>2.0 g/kg
	Skin irritation, rabbit	Primary irritation scores, 6.29 and 4.29
	Eye irritation	Ocular irritation score average = 7.0 (range 4 to 8)
Repeated dose	90-day dermal, rabbit	NOAEL 300 mg/kg/day
Genetic Toxicology – mutation assay	Mouse Lymphoma	Positive
Genetic Toxicology – Clastogenic	Chinese hamster ovary cells	Positive
Reproductive	Two generation rat study (dermal)	No reproductive effects
Developmental	Rat, day 6-15 of gestation (oral)	No teratogenic effects

Appendices